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Further comments on the ascorbic acid requirement

(vitamin C/scurvy/dietary allowances/evolution)

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ABSTRACT **Recommended Daily Allowances (US RDA) of the Food and Drug Administration for ascorbic acid are higher than Recommended Dietary Allowances (set by the Food and Nutrition Board) for adults. There is a 6-fold margin between the requirement to prevent scurvy and the US RDA. The high requirement reported for the rhesus monkey may be needed to compensate for oxidative catabolism of ascorbic acid in this species. The rate of production of ascorbic acid, in mammals that synthesize it, has been listed as 3–19 g/70 kg per day. If this high rate of synthesis represents the requirement of such animals, mutations that caused a loss of ascorbic-acid-synthesizing ability would be eliminated by natural selection on diets that failed to supply these large quantities. The loss of ascorbic-acid-synthesizing ability by human beings could indicate a low requirement, which has enabled our species to spread to regions of the earth where dietary sources of ascorbic acid are poor.**

In an article entitled "Are Recommended Daily Allowances for Vitamin C Adequate?" (1), Pauling discusses the Recommended Dietary Allowance (45 mg) for vitamin C. The article, despite the title, does not mention that the Recommended Daily Allowance (US RDA) of the Food and Drug Administration is 60 mg for an adult (2). The lower level of 45 mg was set by Food and Nutrition Board of the National Academy of Sciences (3), and is not used in labeling regulations. In my article (4), which is criticized by Pauling (1), the adequacy of the Food and Drug Administration recommendation of 60 mg was emphasized.

Pauling says, "*The Food and Nutrition Board has stated in its reports that the RDAs are the amounts of vitamin C and other nutrients that protect against overt manifestations of scurvy and other deficiency diseases, and are not the amounts that lead to the best of health.*" On the contrary the Food and Drug Administration states (3)

> *The Recommended Dietary Allowances are the levels of intake of essential nutrients considered, in the judgment of the Food and Nutrition Board on the basis of available scientific knowledge, to be adequate to meet the known nutritional needs of practically all healthy persons.*

The Food and Nutrition Board, which italicized this statement for emphasis, also addressed itself to the question of the amount of ascorbic acid that protects against overt manifestations of scurvy, as follows:

> *Evidence has been presented and confirmed that a daily intake of 10 mg of ascorbic acid is sufficient to alleviate and cure the clinical signs of scurvy in human subjects (Medical Research Council, 1953; Griffith and Morthland, 1963; Baker et al., 1969, 1971). This amount, however, may not be satisfactory for the maintenance of optimal health over long periods of time.*

Independently of Pauling's opinion on whether or not 10 mg protects against scurvy, the Food and Nutrition Board estimated the antiscorbutic level at 10 mg, and set 45 mg as the Recommended Dietary Allowance, which "*will maintain an adequate body pool of 1,500 mg*". Pauling's version of the Food and Nutrition Board statement is therefore misleading. The allowance is 4.5 times the average amount needed to prevent scurvy. The US RDA, 60 mg, gives an even wider spread between allowances and minimum daily requirements, and supplies a more generous margin than is provided for other nutrients.

Pauling states that Yew (5) "*reported that growth rate and other measures of good health indicate an optimum intake of 3.5 g day^{-1}/70 kg for guinea pigs*", and that "*the extrapolation to man is significant*" *(sic)*. However, Yew's Table 1 and 3 (5) show that the only parameter in which 3.5 g/day per 70 kg was superior to 0.35 g was recovery from anesthesia. Indeed, she states, "*Those at level III*" (3.5 g) "*exhibited higher (growth) rates than those at level II*" (0.35 g) "*and level IV*" (35 g) "*but not significantly so*". In her experiment, 2.31 g, on a different diet, gave better growth than any other level. Yew stated that the highest level (35 g) was "*possibly too high for some of the animals*". This caveat was not cited by Pauling.

An experimentally derived explanation for the higher requirement of ascorbic acid for monkeys than man was provided by Bucci *et al.* (6). They found that the "*paradoxical large daily requirement*" (100–200 mg/10 kg in mulatta monkey) "*appears related to catabolism of ingested ascorbic acid to CO_2 and not to high rate of utilization of ascorbic acid*". They contrast this "*with data in man, with no catabolism to CO_2 . . .*". These findings make it presumptuous to assume that the ascorbic acid requirement of human beings is deducible from the intake of the gorilla (7, 8), and, in any case, the ancestors of man probably dwelled in the open country, rather than in lush tropical forests where succulent leaves and fruit abound.

Pauling (1) states that my criticisms of "*the evolution argument*" seem to have little weight, and that our suggestion (9, 10) that loss of the ability to synthesize ascorbic acid was a neutral evolutionary change in man, fails to explain why this change did not occur for many other species. Various conditions must coincide for a neutral or near-neutral mutation to be incorporated as an evolutionary change, and changes that have been so characterized occur in individual proteins only at long intervals (9, 11, 12). Amino-acid replacements in hemoglobin, for example, are about once in 5.8 million years (13). A mutation that caused loss of the ability to synthesize ascorbic acid could be adopted in evolution only under environmental conditions that furnished a diet supplying the requirement for ascorbic acid. Pauling states that ascorbic-acid-synthesizing mammals produce from 3 to 19 g/70 kg per day, and he concludes that it is unlikely that they would synthesize more "*than the amount required for optimum health*". In such a case, loss of ascor-

Abbreviation: US RDA, Recommended Daily Allowance of the Food and Drug Administration.

bic-acid-synthesizing ability would be highly deleterious, or even lethal, for species such as mice, which are predominantly seed-eaters during the winter, so that mutations to this loss would be eliminated by natural selection. The evolutionary loss of this ability to synthesize ascorbic acid by the human species is therefore a powerful argument, perhaps the most powerful argument, for a low requirement by human beings.

Pauling disagrees with my statement (4) that loss of ascorbic-acid-synthesizing ability in human beings would be "*unlikely unless the ascorbic acid requirement were comparatively small, for the change would greatly restrict the environmental niche that humans would inhabit if their requirements were high*". He says that this statement errs because it implies that an evolutionary change can anticipate a future event. Once the ability to synthesize ascorbic acid is lost, during evolution, to an entire species, the genetic component responsible for the biosynthesis disappears irretrievably. There is no disagreement on this point; the argument is as to whether the requirement, or even the intake, was as high as Pauling suggests. My statement introduced the following two sentences: "*The worldwide spread of our species to numerous localities where dietary sources of ascorbic acid are sparse or seasonal, points to the conclusion that the ascorbic acid requirement is low. Other widely-distributed species, such as ruminants and rats, can synthesize ascorbic acid, so their requirements may be higher than ours*". The loss of the ability to synthesize ascorbic acid obviously could not have anticipated a broadening of the environmental niche, but, because the daily requirement is low, this loss did not prevent the wide migration of human beings into latitudes where the climate is hostile to year-around growth of plants that are the major food source of ascorbic acid.

1. Pauling, L. (1974) *Proc. Nat. Acad. Sci. USA* **71**, 4442–4446.
2. Schmidt, A. M. (1973) *Fed. Regist.* **38**, 20717.
3. Food and Nutrition Board, U.S. National Research Council–National Academy of Sciences (1974) *Recommended Dietary Allowances, National Academy of Sciences, Washington, D.C.*
4. Jukes, T. H. (1974) *Proc. Nat. Acad. Sci. USA* **71**, 1949–1951.
5. Yew, M.-L. S. (1973) *Proc. Nat. Acad. Sci. USA* **70**, 969–972.
6. Bucci, T. J., Johnsen, D. O., Baker, E. M. & Canham, J. E., (1975) *Fed. Proc.* **34**, 883.
7. Bourne, G. H. (1949) *Br. J. Nutr.* **2**, 346.
8. Pauling, L. (1970) *Proc. Nat. Acad. Sci. USA* **67**, 1643.
9. King, J. L. & Jukes, T. H. (1969) *Science* **164**, 788–798.
10. Jukes, T. H. & King, J. L. (1975) *J. Hum. Evol.* **4**, 85–88.
11. Kimura, M. (1968) *Nature* **217**, 624–626.
12. Kimura, M. & Ohta, T. (1974) *Proc. Nat. Acad. Sci. USA* **71**, 2848–2852.
13. Dickerson, R. E. (1971) *J. Mol. Evol.* **1**, 26–45.
14. Dykes, M. H. M. & Meier, P. (1975) *J. Am. Med. Assoc.* **231**, 1073–1079.